(FILE 'HOME' ENTERED AT 15:45:14 ON 22 OCT 2002)

FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 15:45:22 ON 22 OCT 2002

L1 34 S (MITOCHONDRIAL DNA OR MTDNA OR MT DNA) (P) DAMAGE (P) ATHEROS

L2 13 DUP REM L1 (21 DUPLICATES REMOVED)

L3 431 S (MITOCHONDRIAL DNA OR MTDNA OR MT DNA) (P) DAMAGE (P) OXIDATI

L4 174 DUP REM L3 (257 DUPLICATES REMOVED)

L5 171 S L4 NOT L2

L Number	Hits	Search Text	DB	Time stamp
1	340	(mt or mitochondrial) same (dna) same (damage or mutation or deletion$2)	USPAT; US-PGPUB	2002/10/22 15:22
2	8	(mt or mitochondrial) same (dna) same (damage or mutation or deletion$2) same (atherosclero$9)	USPAT; US-PGPUB	2002/10/22 15:23

L2 ANSWER 1 OF 13 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2002119777 MEDLINE
DOCUMENT NUMBER: 21842993 PubMed ID: 11854126
TITLE: Cigarette smoke exposure and hypercholesterolemia increase mitochondrial damage in cardiovascular tissues.
AUTHOR: Knight-Lozano Cynthia A; Young Christal G; Burow David L; Hu Zhao Yong; Uyeminami Dale; Pinkerton Kent E; Ischiropoulos Harry; Ballinger Scott W
CORPORATE SOURCE: Division of Cardiology, University of Texas Medical Branch, Galveston, Tex 77555-1064, USA.
CONTRACT NUMBER: ES011172-01 (NIEHS)
ES09318-1 (NIEHS)
SOURCE: CIRCULATION, (2002 Feb 19) 105 (7) 849-54.
Journal code: 0147763. ISSN: 1524-4539.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 20020221
Last Updated on STN: 20020227
Entered Medline: 20020226

AB BACKGROUND: A shared feature among cardiovascular disease risk factors is increased oxidative stress. Because mitochondria are susceptible to **damage** mediated by oxidative stress, we hypothesized that risk factors (secondhand smoke and hypercholesterolemia) are associated with increased mitochondrial **damage** in cardiovascular tissues. METHODS AND RESULTS: **Atherosclerotic** lesion formation, **mitochondrial DNA damage**, protein nitration, and specific activities of mitochondrial proteins in cardiovascular tissues from age-matched C57 and apoE(-/-) mice exposed to filtered air or secondhand smoke were quantified. Both secondhand smoke and hypercholesterolemia were associated with significantly increased **mitochondrial DNA damage** and protein nitration. Tobacco smoke exposure also resulted in significantly decreased specific activities of mitochondrial enzymes. The combination of secondhand smoke and hypercholesterolemia resulted in increased **atherosclerotic** lesion formation and even greater levels of mitochondrial **damage**. CONCLUSIONS: These data are consistent with the hypothesis that cardiovascular disease risk factors cause mitochondrial **damage** and dysfunction.

L2 ANSWER 2 OF 13 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2002398257 MEDLINE
DOCUMENT NUMBER: 22142252 PubMed ID: 12147534
TITLE: Mitochondrial integrity and function in atherogenesis.
AUTHOR: Ballinger Scott W; Patterson Cam; Knight-Lozano Cynthia A; Burow David L; Conklin Caryl A; Hu Zhaoyong; Reuf Johannes; Horaist Chris; Lebovitz Russell; Hunter Glenn C; McIntyre Ken; Runge Marschall S
CORPORATE SOURCE: Sealy Center for Molecular Cardiology and Division of Cardiology, The University of Texas Medical Branch, Galveston, Tex, USA.
CONTRACT NUMBER: AG10514 (NIA)
ES09318 (NIEHS)

HL03658 (NHLBI)
HL59652 (NHLBI)
SOURCE: CIRCULATION, (2002 Jul 30) 106 (5) 544-9.
Journal code: 0147763. ISSN: 1524-4539.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200208
ENTRY DATE: Entered STN: 20020731
Last Updated on STN: 20020808
Entered Medline: 20020807

AB BACKGROUND: Coronary **atherosclerotic** disease remains the leading cause of death in the Western world. Although the exact sequence of events in this process is controversial, reactive oxygen and nitrogen species (RS) likely play an important role in vascular cell dysfunction and atherogenesis. Oxidative **damage** to the mitochondrial genome with resultant mitochondrial dysfunction is an important consequence of increased intracellular RS. METHODS AND RESULTS: We examined the contribution of mitochondrial oxidant generation and DNA **damage** to the progression of **atherosclerotic** lesions in human arterial specimens and **atherosclerosis**-prone mice. **Mitochondrial DNA damage** not only correlated with the extent of **atherosclerosis** in human specimens and aortas from apolipoprotein E(-/-) mice but also preceded atherogenesis in young apolipoprotein E(-/-) mice. Apolipoprotein E(-/-) mice deficient in manganese superoxide dismutase, a mitochondrial antioxidant enzyme, exhibited early increases in **mitochondrial DNA damage** and a phenotype of accelerated atherogenesis at arterial branch points. CONCLUSIONS: **Mitochondrial DNA damage** may result from RS production in vascular tissues and may in turn be an early event in the initiation of **atherosclerotic** lesions.

L2 ANSWER 3 OF 13 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 3
ACCESSION NUMBER: 2002:72532 BIOSIS
DOCUMENT NUMBER: PREV200200072532
TITLE: **Mitochondrial DNA damage** as a predictor of coronary **atherosclerotic** heart disease.
AUTHOR(S): Runge, Marschall S. (1); Ballinger, Scott W.; VanHouten, Bennett
CORPORATE SOURCE: (1) Galveston, TX USA
ASSIGNEE: Research Development Foundation
PATENT INFORMATION: US 6322974 November 27, 2001
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Nov. 27, 2001) Vol. 1252, No. 4, pp. No Pagination. ftp://ftp.uspto.gov/pub/patdata/. e-file.
ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English

AB The present invention demonstrates that **mitochondrial DNA damage** occurs prior to, or simultaneous with, **atherosclerotic** lesion development, that aortic **mitochondrial DNA damage** increases with age, and that genotype and diet both influence the level of **mitochondrial DNA damage**. Hence, the present invention demonstrates that **mitochondrial DNA**

damage occurs early in **atherosclerosis**, and may be an initiating event in atherogenesis, and provides methods to predict coronary **atherosclerotic** heart disease based upon the amount of **mitochondrial DNA damage**.

L2 ANSWER 4 OF 13 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2001264018 MEDLINE
DOCUMENT NUMBER: 21255155 PubMed ID: 11356636
TITLE: Aging, oxidative responses, and proliferative capacity in cultured mouse aortic smooth muscle cells.
AUTHOR: Moon S K; Thompson L J; Madamanchi N; Ballinger S; Papaconstantinou J; Horaist C; Runge M S; Patterson C
CORPORATE SOURCE: Program in Molecular Cardiology, University of North Carolina, Chapel Hill, North Carolina 27599-7075, USA.
CONTRACT NUMBER: AG-10514 (NIA)
HL-03658 (NHLBI)
HL-57352 (NHLBI)
HL-59652 (NHLBI)
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY. HEART AND CIRCULATORY PHYSIOLOGY, (2001 Jun) 280 (6) H2779-88.
Journal code: 100901228. ISSN: 0363-6135.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010618
Last Updated on STN: 20010618
Entered Medline: 20010614

AB The cellular mechanisms that contribute to the acceleration of **atherosclerosis** in aging populations are poorly understood, although it is hypothesized that changes in the proliferative capacity of vascular smooth muscle cells is contributory. We addressed the relationship among aging, generation of reactive oxygen species (ROS), and proliferation in primary culture smooth muscle cells (SMC) derived from the aortas of young (4 mo old) and aged (16 mo old) mice to understand the phenotypic modulation of these cells as aging occurs. SMC from aged mice had decreased proliferative capacity in response to alpha-thrombin stimulation, yet generated higher levels of ROS and had constitutively increased mitogen-activated protein kinase activity, in comparison with cells from younger mice. These effects may be explained by dysregulation of cell cycle-associated proteins such as cyclin D1 and p27Kip1 in SMC from aged mice. Increased ROS generation was associated with decreased endogenous antioxidant activity, increased lipid peroxidation, and **mitochondrial DNA damage**. Accrual of oxidant-induced **damage** and decreased proliferative capacity in SMC may explain, in part, the age-associated transition to plaque instability in humans with **atherosclerosis**.

L2 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:335402 CAPLUS
DOCUMENT NUMBER: 135:90809
TITLE: High glucose concentrations induce oxidative damage to mitochondrial DNA in explanted vascular smooth muscle cells
AUTHOR(S): Li, Muyao; Absher, P. Marlene; Liang, Ping; Russell, James C.; Sobel, Burton E.; Fukagawa, Naomi K.

CORPORATE SOURCE: Department of Medicine, University of Vermont College of Medicine, Burlington, VT, 05405, USA
SOURCE: Experimental Biology and Medicine (Maywood, NJ, United States) (2001), 226(5), 450-457
CODEN: EBMMBE
PUBLISHER: Society for Experimental Biology and Medicine
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Oxidative stress is considered to be one of the mechanisms leading to atherosclerosis. It occurs in response to injury or to altered metabolic state. Alterations in cell growth (proliferation or apoptosis) can also contribute to the pathogenesis of atherosclerosis and is influenced by oxidative stress. Smooth muscle cells (SMC) from aortic explants of JCR:LA-cp homozygous cp/cp corpulent rats who are genetically predisposed to develop atherosclerosis exhibit increased SMC proliferation, which can be attenuated by exercise and food restriction. This study was conducted to characterize the effects fo oxidative stress and high glucose media on cell growth and its relationship to mitochondrial DNA integrity and gene expression in explanted aortic SMC from corpulent and lean JCR:LA-cp rats.
The results show that SMC from the cp/cp rat appear to be resistant to oxidant-induced cell death and that they accumulate mitochondrial DNA mutations, probably as a result of a redn. in apoptosis. These data suggest that susceptibility to age- and glucose-related atherosclerosis may be related to alterations in redox signaling.
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 6 OF 13 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 2000269965 MEDLINE
DOCUMENT NUMBER: 20269965 PubMed ID: 10807868
TITLE: Hydrogen peroxide- and peroxynitrite-induced mitochondrial DNA damage and dysfunction in vascular endothelial and smooth muscle cells.
COMMENT: Comment in: Circ Res. 2000 May 12;86(9):915-6
AUTHOR: Ballinger S W; Patterson C; Yan C N; Doan R; Burow D L; Young C G; Yakes F M; Van Houten B; Ballinger C A; Freeman B A; Runge M S
CORPORATE SOURCE: Sealy Center for Molecular Cardiology, Division of Cardiology, Sealy Center for Molecular Science, University of Texas Medical Branch, Galveston, Texas, USA.
CONTRACT NUMBER: ES09318 (NIEHS)
HL03658 (NHLBI)
HL59652 (NHLBI)
+
SOURCE: CIRCULATION RESEARCH, (2000 May 12) 86 (9) 960-6.
Journal code: 0047103. ISSN: 1524-4571.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000622
Last Updated on STN: 20010521
Entered Medline: 20000614
AB The mechanisms by which reactive species (RS) participate in the development of **atherosclerosis** remain incompletely understood.

The present study was designed to test the hypothesis that RS produced in the vascular environment cause mitochondrial **damage** and dysfunction in vitro and, thus, may contribute to the initiating events of atherogenesis. DNA **damage** was assessed in vascular cells exposed to superoxide, hydrogen peroxide, nitric oxide, and peroxynitrite. In both vascular endothelial and smooth muscle cells, the **mitochondrial DNA** (**mtDNA**) was preferentially damaged relative to the transcriptionally inactive nuclear beta-globin gene. Similarly, a dose-dependent decrease in **mtDNA**-encoded mRNA transcripts was associated with RS treatment. Mitochondrial protein synthesis was also inhibited in a dose-dependent manner by ONOO(-), resulting in decreased cellular ATP levels and mitochondrial redox function. Overall, endothelial cells were more sensitive to RS-mediated **damage** than were smooth muscle cells. Together, these data link RS-mediated **mtDNA damage**, altered gene expression, and mitochondrial dysfunction in cell culture and reveal how RS may mediate vascular cell dysfunction in the setting of atherogenesis.

L2 ANSWER 7 OF 13 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 2000195316 MEDLINE
DOCUMENT NUMBER: 20195316 PubMed ID: 10733178
TITLE: Biologic activity of mitochondrial metabolites on aging and age-related hearing loss.
AUTHOR: Seidman M D; Khan M J; Bai U; Shirwany N; Quirk W S
CORPORATE SOURCE: Department of Otolaryngology Head & Neck Surgery, Henry Ford Health System, Detroit, Michigan 48323, USA.
SOURCE: AMERICAN JOURNAL OF OTOLOGY, (2000 Mar) 21 (2) 161-7. Journal code: 7909513. ISSN: 0192-9763.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 20000512
Last Updated on STN: 20000512
Entered Medline: 20000503

AB HYPOTHESIS: Compounds that upregulate mitochondrial function in an aging model will improve hearing and reduce some of the effects of aging. BACKGROUND: Reactive oxygen metabolites (ROM) are known products of oxidative metabolism and are continuously generated in vivo. More than 100 human clinical conditions have been associated with ROM, including **atherosclerosis**, arthritis, autoimmune diseases, cancers, heart disease, cerebrovascular accidents, and aging. The ROM are extremely reactive and cause extensive DNA, cellular, and tissue **damage**. Specific deletions within the **mitochondrial DNA** (**mtDNA**) occur with increasing frequency in age and presbyacusis. These deletions are the result of chronic exposure to ROM. When enough **mtDNA damage** accrues, the cell becomes bioenergetically deficient. This mechanism is the basis of the mitochondrial clock theory of aging, also known as the membrane hypothesis of aging. Nutritional compounds have been identified that enhance mitochondrial function and reverse several age-related processes. It is the purpose of this article to describe the effects of two mitochondrial metabolites, alpha-lipoic acid and acetyl L-carnitine, on the preservation of age-related hearing loss. METHODS: Twenty-one Fischer rats, aged 24 months, were divided into

three groups: acetyl-1-carnitine, alpha-lipoic acid, and control. The subjects were orally supplemented with either a placebo or one of the two nutritional compounds for 6 weeks. Auditory brainstem response testing was used to obtain baseline and posttreatment hearing thresholds. Cochlear, brain, and skeletal muscle tissues were obtained to assess for **mtDNA** mutations. RESULTS: The control group demonstrated an expected age-associated threshold deterioration of 3 to 7 dB in the 6-week study. The treated subjects experienced a delay in progression of hearing loss. Acetyl-1-carnitine improved auditory thresholds during the same time period ($p<0.05$). The **mtDNA** deletions associated with aging and presbyacusis were reduced in the treated groups in comparison with controls. CONCLUSIONS: These results indicate that in the proposed decline in mitochondrial function with age, senescence may be delayed by treatment with mitochondrial metabolites. Acetyl-1-carnitine and alpha-lipoic acid reduce age-associated deterioration in auditory sensitivity and improve cochlear function. This effect appears to be related to the mitochondrial metabolite ability to protect and repair age-induced cochlear **mtDNA damage**, thereby upregulating mitochondrial function and improving energy-producing capabilities.

L2 ANSWER 8 OF 13 MEDLINE
ACCESSION NUMBER: 2000490870 MEDLINE
DOCUMENT NUMBER: 20495832 PubMed ID: 11040957
TITLE: The biochemistry of aging.
AUTHOR: Knight J A
CORPORATE SOURCE: Department of Pathology, University of Utah School of Medicine, Salt Lake City, USA.
SOURCE: ADVANCES IN CLINICAL CHEMISTRY, (2000) 35 1-62. Ref: 289
Journal code: 2985173R. ISSN: 0065-2423.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010125

AB Although philosophers and scientists have long been interested in the aging process, general interest in this fascinating and highly important topic was minimal before the 1960s. In recent decades, however, interest in aging has greatly accelerated, not only since the elderly form an ever-increasing percentage of the population, but because they utilize a significant proportion of the national expenditures. In addition, many people have come to the realization that one can now lead a very happy, active, and productive life well beyond the usual retirement age. Scientifically, aging is an extremely complex, multifactorial process, and numerous aging theories have been proposed; the most important of these are probably the genomic and free radical theories. Although it is abundantly clear that our genes influence aging and longevity, exactly how this takes place on a chemical level is only partially understood. For example, what kinds of genes are these, and what proteins do they control?

Certainly they include, among others, those that regulate the processes of somatic maintenance and repair, such as the stress-response systems. The accelerated aging syndromes (i.e., Hutchinson-Gilford, Werner's, and Down's syndromes) are genetically controlled, and studies of them have decidedly increased our understanding of aging. In addition, C. elegans and D. melanogaster are important systems for studying aging. This is especially true for the former, in which the age-1 mutant has been shown to greatly increase the life span over the wild-type strain. This genetic mutation results in increased activities of the antioxidative enzymes, Cu-Zn superoxide dismutase and catalase. Thus, the genomic and free radical theories are closely linked. In addition, trisomy 21 (Down's syndrome) is characterized by a significantly shortened life span; it is also plagued by increased oxidative stress which results in various free radical-related disturbances. Exactly how this extra chromosome results in an increased production of reactive oxygen species is, however, only partially understood. There is considerable additional indirect evidence supporting the free radical theory of aging. Not only are several major age-associated diseases clearly affected by increased oxidative stress (**atherosclerosis**, cancer, etc.), but the fact that there are numerous natural protective mechanisms to prevent oxyradical-induced cellular **damage** speaks loudly that this theory has a key role in aging [the presence of superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase, among others; various important intrinsic (uric acid, bilirubin, -SH proteins, glutathione, etc.) and extrinsic (vitamins C, E, carotenoids, flavonoids, etc.) antioxidants; and metal chelating proteins to prevent Fenton and Haber-Weiss chemistry]. In addition, a major part of the free radical theory involves the damaging role of reactive oxygen species and various toxins on mitochondria. These lead to numerous **mitochondrial DNA** mutations which result in a progressive reduction in energy output, significantly below that needed in body tissues. This can result in various signs of aging, such as loss of memory, hearing, vision, and stamina. Oxidative stress also inactivates critical enzymes and other proteins. In addition to these factors, caloric restriction is the only known method that increases the life span of rodents; studies currently underway suggest that this also applies to primates, and presumably to humans. Certainly, oxidative stress plays an important role here, although other, as yet unknown, factors are also presumably involved. Exactly how the other major theories (i.e., immune, neuroendocrine, somatic mutation, error catastrophe) control aging is more difficult to define. The immune and neuroendocrine systems clearly deteriorate with age. (ABSTRACT TRUNCATED)

L2 ANSWER 9 OF 13 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2000:24536 BIOSIS
DOCUMENT NUMBER: PREV200000024536
TITLE: Cigarette smoke causes increased **mitochondrial DNA damage** and **atherosclerotic** lesion formation in apolipoprotein E null mice.
AUTHOR(S): Knight, Cynthia A. (1); Hu, Zhaoyong (1); Burow, David L. (1); Horaist, Chris (1); Pinkerton, Kent; Ballinger, Scott W.
CORPORATE SOURCE: (1) Univ of Texas Med Branch, Galveston, TX USA
SOURCE: Circulation, (Nov. 2, 1999) Vol. 110, No. 18 SUPPL., pp.

I.259.
Meeting Info.: 72nd Scientific Sessions of the American Heart Association Atlanta, Georgia, USA November 7-10, 1999
ISSN: 0009-7322.
DOCUMENT TYPE: Conference
LANGUAGE: English

L2 ANSWER 10 OF 13 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1998:18522 BIOSIS
DOCUMENT NUMBER: PREV199800018522
TITLE: In vivo evidence of the relationship of reactive oxygen species and **mitochondrial DNA damage** in **atherosclerosis.**
AUTHOR(S): Yan, Chang-Ning; Ballinger, Scott; Vanhouten, Bennett; Ruef, Johannes; Doan, Richard; Li, Fengzhi; Horaist, Christopher K.; Patterson, Cam; Runge, Marschall S.
CORPORATE SOURCE: Univ. Texas, Galveston, TX USA
SOURCE: Circulation, (10/21/97, 1997) Vol. 96, No. 8 SUPPL., pp. I604.
Meeting Info.: 70th Scientific Sessions of the American Heart Association Orlando, Florida, USA November 9-12, 1997
ISSN: 0009-7322.
DOCUMENT TYPE: Conference
LANGUAGE: English

L2 ANSWER 11 OF 13 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:275003 CAPLUS
DOCUMENT NUMBER: 126:275203
TITLE: Glutathione, oxidative stress and aging
AUTHOR(S): Sastre, Juan; Pallardo, Federico V.; Via, Jose
CORPORATE SOURCE: Department of Physiology, Faculty of Medicine, University of Valencia, Spain
SOURCE: Age (Chester, Pennsylvania) (1996), 19(4), 129-139
CODEN: AGEEDB; ISSN: 0161-9152
PUBLISHER: American Aging Association
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review and discussion with 104 refs. The free radical theory of aging proposes that the impairment in physiol. performance assocd. with aging is caused by the detrimental effects of O free radicals. This is interesting because it provides a theor. framework to understand aging and because it suggests a rationale for intervention, i.e., antioxidant administration. Thus, the study of antioxidant systems of the cell may be very important in gerontol. studies. Glutathione is one of the main nonprotein antioxidants in the cell which, together with its related enzymes, constitute the glutathione system. The involvement of glutathione in aging has been known since the early seventies. Several studies have reported that reduced glutathione is decreased in cells from old animals, whereas oxidized glutathione tends to be increased. Recent expts. from the authors' lab. have underscored the importance of cellular compartmentation of glutathione. Mitochondrial glutathione plays a key role in the protection against free radical **damage** assocd. with aging. Oxidative **damage** to **mitochondrial DNA** is directly related to oxidn. of mitochondrial glutathione. In fact, aging is assocd. with oxidative **damage** to proteins, nucleic acids, and lipids. These mol. lesions may be responsible for the low

physiol. performance of aged cells. Thus, antioxidant supplementation may be a rational way to partially protect against age-assocd. impairment in performance. Apoptosis, a programmed cell death, is an area of research which has seen an explosive growth. Glutathione is involved in apoptosis: apoptotic cells have lower levels of reduced glutathione, and administration of glutathione precursors prevent, or at least delay, apoptosis. Age-assocd. diseases constitute a major concern for researchers involved in aging. Free radicals are involved in many such diseases, e.g., cancer, diabetes, or **atherosclerosis**. The key role of glutathione and other antioxidants in the pathophysiol. of aging and age-assocd. diseases is discussed.

L2 ANSWER 12 OF 13 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 97046944 MEDLINE
DOCUMENT NUMBER: 97046944 PubMed ID: 8891865
TITLE: The role of mitochondria in ischemic heart disease.
AUTHOR: Ferrari R
CORPORATE SOURCE: Cattedra di Cardiologia, Universita' degli Studi di Brescia, Italy.
SOURCE: JOURNAL OF CARDIOVASCULAR PHARMACOLOGY, (1996) 28 Suppl 1 S1-10. Ref: 80
Journal code: 7902492. ISSN: 0160-2446.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970219
Last Updated on STN: 20000303
Entered Medline: 19970123

AB Mitochondria in the heart play two roles essential for cell survival: ATP synthesis and maintenance of Ca2+ homeostasis. These two processes are driven by the same energy source, the H+ electrochemical gradient (delta microH). Under aerobic physiologic conditions, mitochondria do not contribute to the beat-to-beat regulation of cytosolic Ca2+, although a Ca2+ transient in mitochondrial matrix has been described. Micromolar increases in mitochondrial Ca2+ concentration stimulate the Krebs cycle and the NADH redox potential and, therefore, ATP synthesis. Trimetazidine has been shown to improve the calcium transient and, in so doing, the overall myocardial energy production. Under pathologic conditions, mitochondrial Ca2+ overload causes a series of vicious cycles that lead to irreversible cell **damage**. During ischemia, an alteration in intracellular Ca2+ homeostasis occurs and mitochondria are able to buffer cytosolic Ca2+, suggesting that they retain the Ca(2+)-transporting capacity. Accordingly, once isolated, even after prolonged ischemia the majority of the mitochondria are able to use oxygen for ATP phosphorylation. When isolated after reperfusion, mitochondria are structurally altered, contain large quantities of Ca2+, and produce an excess of oxygen free radicals. Their membrane pores are stimulated and the capacity for oxidative phosphorylation is irreversibly disrupted. The role of **mitochondrial DNA damage** in progressive human diseases such as coronary **atherosclerosis** is receiving growing interest. The sequence of ischemia and reperfusion, through increased production of oxygen free radicals, causes mitochondrial

deletions in several areas of the mitochondrial genome. This cumulative **mitochondrial DNA damage** is associated with induction of nuclear oxidative phosphorylation gene mRNA. These observations support the hypothesis that mitochondria and **mitochondrial DNA damage** play important roles in ischemic heart disease.

L2 ANSWER 13 OF 13 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 93024614 MEDLINE
DOCUMENT NUMBER: 93024614 PubMed ID: 1383759
TITLE: Association of **mitochondrial DNA damage** with aging and coronary **atherosclerotic** heart disease.
AUTHOR: Corral-Debrinski M; Shoffner J M; Lott M T; Wallace D C
CORPORATE SOURCE: Department of Genetics and Molecular Medicine, Emory University School of Medicine, Atlanta, GA 30322.
CONTRACT NUMBER: HL45572 (NHLBI)
NS01336 (NINDS)
SOURCE: MUTATION RESEARCH, (1992 Sep) 275 (3-6) 169-80. Ref: 52
Journal code: 0400763. ISSN: 0027-5107.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199211
ENTRY DATE: Entered STN: 19930122
Last Updated on STN: 19960129
Entered Medline: 19921123

AB The role of somatic **mitochondrial DNA** (**mtDNA**) **damage** in human aging and progressive diseases of oxidative phosphorylation (OXPHOS) was examined by quantitating the accumulation of **mtDNA** deletions in normal hearts and hearts with coronary **atherosclerotic** disease. In normal hearts, **mtDNA** deletions appeared after 40 and subsequently accumulated with age. The common 4977 nucleotide pair (np) deletion (mtDNA4977) reached a maximum of 0.007%, with the mtDNA7436 and mtDNA10,422 deletions appearing at the same time. In hearts deprived of mitochondrial substrates due to coronary artery disease, the level of the mtDNA4977 deletion was elevated 7-220-fold over age-matched controls, with the mtDNA7436 and mtDNA10,422 deletions increasing in parallel. This cumulative **mtDNA damage** was associated with a compensatory 3.5-fold induction of nuclear OXPHOS gene mRNA and regions of ischemic hearts subjected to the greatest work load (left ventricle) showed the greatest accumulation of **mtDNA damage** and OXPHOS gene induction. These observations support the hypothesis that **mtDNA damage** does accumulate with age and indicates that respiratory stress greatly elevates mitochondrial **damage**.

L Number	Hits	Search Text	DB	Time stamp
1	303	mitochondrial same damage	USPAT	2002/10/21 13:09
2	12454	atherosclero$8	USPAT	2002/10/21 13:10
3	10	(mitochondrial same damage) same atherosclero$8	USPAT	2002/10/21 13:12
4	35	mdna	USPAT	2002/10/21 13:12
5	9	mdna and damage	USPAT	2002/10/21 13:12
6	0	mdna same damage	USPAT	2002/10/21 13:12

(FILE 'HOME' ENTERED AT 07:17:32 ON 16 NOV 2002)

FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 07:17:51 ON 16 NOV 2002

```
L1             6 S RUNGE/AU
                 E RUNGE/AU
                 E RUNGE M/AU
L2           343 S E3
L3           389 S E10
L4           210 S E20-E23
L5           948 S L1 OR L2 OR L3 OR L4
L6            27 S L5 AND DAMAGE
L7            16 DUP REM L6 (11 DUPLICATES REMOVED)
L8         49858 S MITOCHONDRIAL DNA OR MTDNA
L9       1114516 S DAMAGE OR DELETION
L10         7897 S L8 AND L9
L11        94143 S OXIDATIVE STRESS
L12          852 S L10 AND L11
L13         7084 S L8 (P) L9
L14         4760 S L8 (5A) L9
L15          572 S L11 AND L14
L16           90 S L15 AND PCR
L17           45 DUP REM L16 (45 DUPLICATES REMOVED)

=>
```